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Dr. M.G.P. Stoker
Director of Research
Imperial Cancer Research
Fund Laboratories
P.O. Box 123
Lincoln's Inn Fields
London, WC2A 3PX
England

Dear Michael:

Thank you for taking the time to write your well-reasoned letter of October 18. As I indicated to the Macy Foundation (in response to their concern about my priorities) and to Mike Fried, I have come to more or less the position you have advised, although for somewhat different reasons. The hepatitis work seems out at present, in part because I am having difficulties assembling the necessary reagents; I am now planning to begin work in earnest on this problem only after I return and have developed suitable facilities here. I am also somewhat discouraged by the bureaucratic hurdles that stand between me and the cloning of integration sites for various RNA tumor viruses, though I still believe a good case can be made for a Category 3 assignment for several such experiments. I have sensed a lack of enthusiasm on this subject in Mike Fried's letters, which I now understand more fully in the light of your letter. We are continuing to explore other ways to get some of the appropriate clones made, either here or abroad, depending upon P4 facilities, new guidelines, etc. For the moment, I would simply like to learn to do cloning in a polyoma vector, since this may be the best way to do a variety of things here in the absence of a P4 facility or an EK3 system. I have written and will again write to Mike Fried about my interest in giving him a hand with anything he is doing, in order to become familiar with the polyoma system. Of the three original proposals, I am left with the production of deletion mutants of avian leukosis viruses. Although it's perfectly possible that something else will seem more attractive by the time I arrive, this still seems fine to me at the present. However, I would prefer to be based in the polyoma group (i.e., in Mike Fried's lab) for this work for several reasons: (1) I foresee needing more day-to-day advice about the enzymatic manipulations than about the growth of viruses with which I am rather familiar; (2) I hope to be doing some work with Mike to learn the polyoma system, as noted above; and (3) I think I will learn more during the year if surrounded by people I know less well working on a system I know less about. Naturally, I shall be very grateful for advice from John and Robin, but I see the problem initially as one in nucleic acid biochemistry with clear precedents in the papovavirus systems. I have, in fact, recently discussed these plans with Phil Neiman who has some interest in attempting to develop <u>in vitro</u> assays for avian leukosis viruses while in Robin's lab; if we were both successful, it would obviously be nice to test my mutants in his assays, but that seems a long way off.

Certainly I think these plans are sufficiently ill-formed and my arrival sufficiently

distant that further discussion with all the parties possibly concerned can await next summer. In the meantime, I shall write to Mike Fried in the hopes that he will be amenable to the proposals I have laid out here. I am sensitive to the possibility that my ambiguities about projects and location may have aggrevated rather than avoided some difficulties I had anticipated about settling in at ICRF. I hope that I can now resolve some of these uncertainties without unduly upsetting anyone.

Incidentally, you may have noticed that the issue of Nature which brought me the good news that you would be at ICRF during my year there also contained the person-to-person item from me that you had also recommended. Although I have had no responses to it as yet, we have had several interesting---and a few promising---responses to other inquires and advertisements. As a result, at the moment, I am feeling fairly secure about the domestic situation.

I will keep you informed of further developments.

With best personal regards,

Harold E. Varmus, M.D.
Associate Professor
Department of Microbiology

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